CESIUM INCREASES INTRACELLULAR UPTAKE OF $^{45}Ca^{2+}$ AND INCREASES FORCE DEVELOPMENT IN CARDIAC VENTRICULAR MUSCLE DURING THE EVOLUTION OF EARLY AFTER-DEPOLARIZATIONS.

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Low, nondepolarizing concentrations of Cs^+ may induce early after-depolarizations (L-EAD) which occur at terminal phases of the repolarization of action potentials at voltage levels negative to -60 mV. Earlier observations indicated that L-EAD develop with a delay after the administration of Cs^+ during which time Ca^{2+} could accumulate in intracellular compartments. This observation suggested that L-EAD may develop only if the myocardium is sufficiently loaded with Ca^{2+}. To test this hypothesis we studied the effects of Cs^+ on intracellular $^{45}Ca^{2+}$ uptake and on the force development and relaxation of contraction with the same conditions that induced L-EAD. Rings (1mm) from both ventricles were stimulated at 0.2 Hz during 30 min of superfusion at 37°C with solution containing $^{45}Ca^{2+}$. Cs^+ (4.0mM) increased $^{45}Ca^{2+}$ uptake (nmol/g/30min ± SE) from 566±24 to 1102±63 ($p<0.001$) in 15 rings from right ventricles and from 375±14 to 816±30 ($p<0.001$) in 26 rings from left ventricles. Peak tension developed in papillary muscles increased from 13±0.8 to 19±6.3 mN/cm^2 with Cs treatment. The maximal rate of force development increased from 0.110±0.01 to 0.193±0.03 mN/cm^2/msec. The half relaxation time reduced from 91±5 to 68±2 msec. The total mechanical output remained unchanged (control: 744±10; Cs^+: 723±10.4 mN/cm^2). Thus Cs^+ augments intracellular Ca^{2+} uptake and enhances Ca^{2+} release and kinetics from sarcoplasmic reticulum, suggesting a relationship between L-EAD and Ca^{2+} loading.

CORONARY BLOOD PRESSURE MODULATES ATRIAL NATRIURETIC FACTOR DISTRIBUTION IN HYPERTROPHIED RAT VENTRICULES

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In several models of hemodynamic overload, in rats, increases of arterial and coronary blood pressures and ventricular hypertrophy are known to activate Atrial Natriuretic Factor (ANF) gene expression, but results from previous studies were unable to distinguish between these two factors. To provide evidence for a direct effect of coronary blood pressure, independent of hypertrophy, we investigated, by immunocytochemistry using specific polyclonal anti-ANF antibodies, the presence and the distribution of ANF in two hypertrophied ventricles models : thoracic aortic stenosis (AS) and aortic incompetence (AI) which have respectively a high and a low coronary perfusion pressure. 30 rats were studied (10 sham, 10 AS, 10 IA). In sham-operated animals, ANF was only present in atria. Bright ANF immunoreactivity was observed in hypertrophied left ventricules (LV) following AS especially in the smooth muscle cells of the coronary vessels. Conversely, in hypertrophied LV following AI, ANF immunoreactivity was restricted to the atrial myocytes and never was observed in either smooth muscle cells nor striated myocytes of the ventricles.

Our data suggest that increased coronary artery pressure is an important trigger for ANF activation in overloaded ventricles rather than the hypertrophy process.

Tuesday, March 20, 1990
10:30AM–12:00NOON, Room 26
Congenital Heart Disease

ATRIAL NATRIURETIC FACTOR PREVENTS RADIOCONTRAST-INDUCED NEPHROPATHY IN DOGS WITH EXPERIMENTAL HEART FAILURE.

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Radiocontrast-induced nephropathy (RCIN) is an important cause of acute renal failure with no effective treatment. Recognizing the high incidence of RCIN in humans with congestive heart failure (CHF), this study was designed to test the hypotheses that dogs with experimental CHF are at increased risk of RCIN and that synthetic atrial natriuretic factor (ANF) can prevent RCIN in this model. Three groups of 5 conscious, non-instrumented dogs received radiocontrast (iothalamate meglumine 52% and iothalamate sodium 26%) 7 ml/kg intravenously. Group I dogs were normal controls. Both group II and group III dogs had experimental CHF induced by 8 days of ventricular pacing at 250 beats per minute. Group III dogs received an infusion of suprarenal ANF (30 ng/kg/min) for one hour before, during and after the infusion of radiocontrast to achieve intrarenal plasma ANF levels of 1200 to 2000 pg/ml. Creatinine clearance was measured daily in all dogs.

Days post contrast	Change in Creatinine Clearance from Baseline (ml/min) Gp I-normal	Gp II-CHF	Gp III-CHF+ANF
1	+10±6	-6±8	+15±20
2	+4±3	-25±7*†	+2±7
3	+10±5	-22±7*†	+10±8
4	+6±4	-15±3*†	+6±4
5	+9±8	-20±6*†	+4±6
6	+13±6	-10±7	+8±10

(* = $p < 0.05$ vs. baseline; † = $p < 0.05$ vs. other groups)

A decrease in creatinine clearance was observed in group II (CHF), with the greatest decrease 2 days after radiocontrast and a tendency to recover thereafter. There was no decrease in creatinine clearance following radiocontrast in group I(normal) and group III(CHF+ANF). In conclusion, experimental CHF is a risk for RCIN and therefore may provide a clinically relevant model of RCIN. Pharmacologic intrarenal levels of ANF prevent RCIN in this model of experimental CHF.

SPONTANEOUS AND EVOKED RELEASE OF ATRIAL NATRIURETIC PEPTIDE FROM THE RAT ATRIA IN VITRO.

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The characteristics of atrial natriuretic peptide (ANP) release from rat atria and ventricular tissues were investigated in vitro. The experiments consisted of superfused sliced tissues (300µm) with Krebs-buffer (0,1ml/min) continuously gassed with O2/CO2 (95%/5%). After 45 min of equilibrium the superfusing fluids were collected at 5 min intervals for immunoreactive ANP determinations.

Under normal ionic conditions (K^+=4mM, Na^+=139mM), right atria released immunoreactive ANP-like material at a rate of 32.9 ± 4.2 pg/min/mg of tissue. This value was significantly higher compared with left atria (11.6 ± 2.7 pg/min/mg of tissue, $p<0,001$) or ventricular preparations (1.10 ± 0.5 pg/min/mg of tissue). Gel filtration chromatographic analysis in Sephadex G50 indicate that 86% of this immunoreactive material had the same antigenic determinant and behaved as the authentic α-ANP.

Addition of Na^+ or K^+ (30mM to 100mM) to the superfusing fluid resulted in a significant increase (respectively +113% and +153 %) in the peptide outflow from right atria in a dose-dependent manner. Similar result was obtained with 10^{-5} M vasopressin (AVP)(+128 %).

Thus, our superfusion method is a reliable and dynamic approach of the release of ANP from heart tissue following physiological or pharmacological stimuli in vitro. Our results suggest a ionic (K^+, Na^+) or an humoral control (AVP) of the atrial ANP release independent of the atrial stretch.